IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5256
WILLIAMS *et al.*	Art Unit: 1652
Appl. No.: 09/839,946	Examiner: Saidha, T.
Filed: April 19, 2001	Atty. Docket: 2057.0090003/JAG/BJD
For: **PEG-Urate Oxidase Conjugates and Use Thereof**	

Declaration of Merry R. Sherman Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, **Merry R. Sherman,** declare and state that:

1. I am a co-inventor of the above-captioned U.S. patent application number 09/839,946, filed April 19, 2001, entitled, "PEG-Urate Oxidase Conjugates and Use Thereof."

2. I am also the President of Mountain View Pharmaceuticals, Inc. ("MVP"), a co-assignee of the present application by virtue of an assignment from L. David Williams, Mark G. P. Saifer and Merry R. Sherman to MVP executed on September 29, 1999, and recorded in the U.S. Patent and Trademark Office on November 30, 2001, beginning at Reel No. 012320, Frame No. 0564.

3. My *curriculum vitae* is attached as **Exhibit A.**

4. I have reviewed the above-identified patent application and the Office Action dated January 26, 2005. I would like to address certain remarks raised by Examiner Saidha in the Office Action.

5. On page 2 of the Office Action, Examiner Saidha states that Lee *et al.* (hereinafter "Lee") discloses that mammalian uricase is a "tetramer with subunit size of 32,000 daltons." The Examiner uses this statement in Lee to support his assertion that the mammalian uricase in Lee was 100% in the tetrameric form. However, the mammalian uricase referred to by Lee, in the sentence pointed out by the Examiner, refers to mammalian uricase "associated with the peroxisome." The mammalian uricase "associated with the peroxisome" is very different from the purified mammalian uricase disclosed by Lee. Specifically, while mammalian uricases *in vivo* (*i.e.*, associated with the peroxisome) exist as a tetramer, isolated purified preparations of natural and recombinant uricase, as indicated in the present specification and as disclosed by Lee, usually contain a mixture of aggregated non-tetrameric forms of the enzyme, in addition to the tetrameric form. *See* specification at page 16, lines 5-8.

6. As explained in the present specification, a mixture of various aggregated forms of the uricase, other than the tetrameric form, is believed to be highly immunogenic. *See* specification at page 16, lines 8-16. However, the present application teaches a method for isolating a tetrameric form of uricase from a solution containing natural and/or recombinant forms of uricase, thereby reducing the immunogenicity of the uricase without disrupting its activity. *See* specification at page 10, lines 15-29. The purification procedure, as outlined in the present specification, results in the chromatographic results shown in attached Figures 1 and 2. Figures 1 and 2, attached hereto, were disclosed in U.S Patent No. 6,783,965 ("the '965 patent") as Figures 2 and 3. MVP is the assignee of the '965 patent.

7. Figure 1 illustrates size exclusion HPLC analysis on a Pharmacia Superdex 200 column (1x30 cm) of the load and selected fractions from a preparative Mono Q chromatography of porcine uricase containing the mutations R291K and T301S (PKS uricase) showing data obtained by a light scattering detector at 90°C (upper curves) and by absorbance at 276 nm (lower curves). Figure 2 illustrates size-exclusion analyses of fractions from a Mono Q column, showing data obtained by a light scattering detector at 90° and by absorbance at 276 nm, as in Figure 1.

8. The top panel in each of Figures 1 and 2 illustrates that octamers and larger non-tetrameric aggregates account for greater than 10% of the uricase present in isolated natural and recombinant uricase preparations, such as those disclosed in Lee. After the purification procedure of the present application is performed, the majority (*i.e.*, at least about 90%) of the uricase present is in a tetrameric form. *See* bottom panel in each of Figures 1 and 2. Thus, these data clearly demonstrate that the purification procedures disclosed in the present application are required in order to obtain the presently claimed isolated mammalian uricases in which at least about 90% of the uricase is in the tetrameric form. Accordingly, without specifically purifying their uricase preparations according to the methods of the present application, the authors of Lee would not be expected to have produced an uricase preparation in which at least about 90% of the uricase is in a tetrameric form.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements

and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

Merry R. Sherman, Ph.D.

Date: May 25, 2005

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EXHIBIT A

MERRY RUBIN SHERMAN, PH.D.
President
Mountain View Pharmaceuticals, Inc.

Education:

Wellesley College, Wellesley, MA	B.A.	1961	Chemistry
University of California, Berkeley, CA	M.A.	1963	Biochemistry
University of California, Berkeley, CA	Ph.D.	1966	Biophysics
Weizmann Institute, Rehovot, Israel	Postdoctoral	1966-1967	Polymer Science
National Institutes of Health, Bethesda, MD	Fellowships	1967-1970	Biochemistry

Research Positions:

1970-1976 Research Associate and Associate, Department of Surgical Research, Sloan-Kettering Institute (SKI), New York, NY

1975-1976 Visiting Investigator, Cardiovascular Research Institute, University of California Medical Center, San Francisco, CA

1975-1986 Head, Endocrine Biochemistry Laboratory, SKI

1/92-8/92 Visiting Scientist, New York University Medical Center, New York, NY

1993-1995 Pharmaceutical Consultant, Mountain View, CA

1995-present President, Mountain View Pharmaceuticals, Inc.

Academic Positions: *Positions at Cornell University Graduate School of Medical Sciences (CUGSMS), New York, NY, were concurrent with those at SKI*

1971-1972 Instructor in Biochemistry, CUGSMS, New York, NY

1972-1977 Assistant Professor of Biochemistry, CUGSMS

1977-1986 Associate Professor of Biochemistry, CUGSMS

1986-1993 Professor of Biochemistry, Rutgers University, Newark, NJ

Honors:

1957 Finalist, National Science Talent Search

1960 Elected to *Phi Beta Kappa*

1985 Outstanding Woman Scientist Award, Association for Women in Science, Metropolitan New York Chapter

1987 Distinguished Alumna Award, New Rochelle High School, New Rochelle, NY

Editorial Boards and Refereeing:

1974-1978 Editorial Board, *Endocrine Research Communications*

7/78-6/81 Editorial Board, *Journal of Biological Chemistry*

7/82-6/84 Editorial Board, *Journal of Biological Chemistry*
Occasional reviews for:
Anal Biochem, Arch Biochem Biophys, Biochemistry, Cancer Research, Endocrinology, Nature, Proc Natl Acad Sci USA, Steroids

Special NIH Study Sections: 2/77, 1/79, 12/82, 5/85 and 4/91

National Committees:

9/84-6/88 Program Committee of The Endocrine Society

12/85-6/88 Board of Scientific Counselors, Natl. Institute of Child Health and Human Dev.

Professional Memberships: American Society of Biological Chemists, The Endocrine Society, American Association for Cancer Research, Society for Neuroscience, Association for Women in Science, American Association of Pharmaceutical Scientists.

Selected Publications:

Rubin MM, Katchalsky A (1966) Mathematics of band centrifugation: Concentration-independent sedimentation and diffusion in shallow density gradients. Biopolymers 4:579-593.

Rubin MM, Changeux J-P (1966) On the nature of allosteric transitions: Implications of non-exclusive ligand binding. J Mol Biol 21:265-274.

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Sherman MR, Corvol PG, O'Malley BW (1970) Progesterone-binding components of chick oviduct. I. Preliminary characterization of cytoplasmic components. J Biol Chem 245:6085-6096.

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Sherman MR, Moran MC, Tuazon FB, Stevens Y-W (1983) Structure, dissociation, and proteolysis of mammalian steroid receptors. Multiplicity of glucocorticoid receptor forms and proteolytic enzymes in rat liver and kidney cytosols. J Biol Chem 258:10366-10377.

Sherman MR, Tuazon FB, Stevens Y-W, Niu E-M (1983) Oligomeric steroid receptor forms and the products of their dissociation and proteolysis. *in:* Steroid Hormone Receptors: Structure and Function, Proceedings of the 57th Nobel Symposium, Karlskoga, Sweden, 1983, (Eriksson H, Gustafsson J-Å, *eds.*). Amsterdam, Elsevier, pp. 3-24.

Sherman MR, Stevens Y-W, Tuazon FB (1984) Multiple forms and fragments of cytosolic glucocorticoid receptors from human leukemic cells and normal lymphocytes. Cancer Research 44:3783-3796.

Sherman MR, Stevens J (1984) Structure of mammalian steroid receptors: Evolving concepts and methodological developments. Annu Rev Physiol 46:83-105.

Gorsline J, Bradlow HL, Sherman MR (1985) Triamcinolone acetonide 21-oic acid methyl ester: A potent local antiinflammatory steroid without detectable systemic effects. Endocrinology 116:263-273.

Maayani S, Sherman M R (1990) Adenylate cyclase-linked 5-hydroxytryptamine receptors in the brain. *in:* Serotonin: From Cell Biology to Pharmacology and Therapeutics, (Paoletti R, Vanhoutte PM, Brunello N, Maggi FM, *eds.*). Dordrecht, The Netherlands, Kluwer Academic Publishers, pp. 39-51.

Smith R A, Balis F M, Ott K H, Elsberry D D, Sherman M R, Saifer M G P (1995) Pharmacokinetics and tolerability of ventricularly administered superoxide dismutase in monkeys and preliminary clinical observations in familial ALS. J Neurol Sci 129 (Suppl): 13-18.

Saifer M G P, Williams L D, Sherman M R, French J A, Kwak L W, Oppenheim J J (1997) Improved conjugation of cytokines using high molecular weight poly(ethylene glycol): PEG-GM-CSF as a prototype. Polymer Preprints 38:576-577.

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Diabetes insipidus in uricase-deficient mice: A model for evaluating therapy with poly(ethylene glycol)-modified uricase. J Am Soc Nephrol 12:1001-1009.

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Sherman MR, Martinez AL, Bhaskaran SS, Williams LD, Saifer MGP, French JA (2003) Polymer conjugates of proteinases. US Patent Application No. 2003/0012777 A1, Mountain View Pharmaceuticals, Inc., published Jan. 16, 2003.

Williams LD, Hershfield MS, Kelly SJ, Saifer MGP, Sherman MR (2003). PEG-urate oxidase conjugates and use thereof. US Patent No. 6,576,235 B1, Mountain View Pharmaceuticals, Inc., Jun. 10, 2003.

Martinez AL, Sherman MR, Saifer MGP, Williams LD (2004) Polymer conjugates with decreased antigenicity, methods of preparation and uses thereof. US Patent Application No. 2004/0062746 A1, Mountain View Pharmaceuticals, Inc., published Apr. 1, 2004.

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Saifer MGP, Martinez AL, Williams LD, Sherman MR (2004) Polymer conjugates of interferon-beta with enhanced biological potency. US Patent Application No. 2004/0126361 A1, Mountain View Pharmaceuticals, Inc., published Jul. 1, 2004.

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Bhaskaran SS, Sherman MR, Saifer MGP, Williams LD (2004) Polymer conjugates of cytokines, chemokines, growth factors, polypeptide hormones and antagonists thereof with preserved receptor-binding activity. PCT Patent Publication No. WO 2004/060300 A2, Mountain View Pharmaceuticals, Inc., published Jul. 22, 2004.

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